Risk of Spaceflight-Induced Intracranial Hypertension / Vision Alterations

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Disclosures

Within the last 12 months:

- I receive grant support from NeuroDx Development for work related to SBIR R43NS067770-01A1
- I receive grant support from the National Space Biomedical Research Institute (NSBRI) for projects SMST02802 and CA02801
- 5% interest in Mensana Therapeutics, LLC
- My spouse owns stock in Ecolab, GE, Life Technologies, Medtronic, and Pfizer
My Perspective and Role

- I have studied intracranial pressure (ICP) for my entire career since going to Johns Hopkins in 1989 for a NeuroICU fellowship.
- I use ICP monitoring routinely in the diagnosis and treatment of disorders of CSF circulation, including:
  - Pseudotumor cerebri (the VIIP exemplar)
  - Hydrocephalus
  - Shunt malfunction
- I have an NSBRI grant to validate noninvasive ICP methods.
Response to the Panel’s Questions

- Is the pathogenesis of the condition established? **No**
- Is there evidence that ground-based models can reproduce the spaceflight conditions that lead to this vision problem? **No**
- Does the evidence support planning for risk mitigation? **No**
- Does the evidence report provide sufficient evidence that the risk is of concern for long-term space missions? **Probably**
Response to the Panel’s Questions

- Are there additional gaps in knowledge or areas of fundamental research that should be considered to enhance the understanding of this risk? **Yes**

- What are the major sources of disagreement in the literature about this risk? **None exists**

- What is known about interactions between this risk and other spaceflight health risks identified in NASA’s evidence reports? Does the evidence report address relevant interactions among risks? **Unknown**
My list of critical questions

- Is this really a disorder of ICP?
- Is CSF circulatory physiology altered by long-term exposure to microgravity? If so, how?
- Is VIIP risk related to total time in space?
- Why does CSF pressure remain elevated after astronauts return to earth?
- Is VIIP reversible or irreversible?
- How do we measure ICP in space?
- Can we identify astronauts at risk?
- If so, can we prevent or treat VIIP in space?
My Approach to the Review

- I decided to review the report as if it were submitted for peer-reviewed publication.
- I paid particular attention to:
  - The data and hypotheses presented and the conclusions reached.
  - Internal coherence or inconsistency.
  - Use of citations and reference to the existing literature.
  - I am addressing primarily the ICP issue.
- I am fairly critical because of the high stakes, expense and timeline.
General Comments on the Report

Generally well-written, however:

- Internally inconsistent and sometimes contradictory
- Reasoning reflects an incomplete understanding of cerebrovascular physiology, CSF circulation, and CSF hydrodynamics
- Imprecise language (e.g. pooling, stagnating) vs a misunderstanding of concepts
- Implausible cause / effect relationships
- Misreading or misquoting of some references
Over-extrapolation from animal models, short-term parabolic flight studies, or “drop” studies to long-term hypotheses

Incomplete integration of known zero-G physiology into the ICP and CBF hypotheses

Failure to understand the difference between acute and chronic changes of FiCO₂, PaCO₂, and ETCO₂ on ICP, and failure to account for the effect of renal acid-base buffering on the influence of hypercapnea on ICP
Reliance on uncertain MR-ICP and (especially) MR-CSF production methods

Attributing vascular engorgement to increased pressure when NASA’s data shows it can be due to changes in compliance due to zero G

Incomplete integration of the fact that there is, or should be, no hydrostatic pressure gradient in zero G, which means that ICP dynamics should be equivalent to the supine / horizontal position in 1 G
In relation to ICP and CSF circulation, the report is:

All hypothesis and no data
Is this really a disorder of ICP?

- Unclear and unresolved from the physiologic hypothesis perspective
- Papilledema does not require ICP elevation
- Dilation of the optic nerve sheath could be volume redistribution rather than pressure related
- Evidence from cardiovascular physiology in microgravity suggests that jugular venous dilation occurs in the absence of elevated CVP
- CVP influences SSSP which influences ICP
Veins collapse if: $P_{\text{vein}} < \text{atmospheric pressure}$

Davson equation: $\text{ICP} = q_f * R_{\text{out}} + P_{SS}$

$P_{SS} = CVP$

$\text{ICP}_{up} = q_f * R_{\text{out}} + \rho g h$

Veins collapse if: $P_{\text{vein}} < \text{atmospheric pressure}$

$\text{ICP}_{sup} = q_f * R_{\text{out}} + CVP$

$h_{eff}$

$h$

Slide courtesy Anders Eklund, Jan Malm
Postural effects on intracranial pressure: modeling and clinical evaluation

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Submitted 19 June 2013. Revision received 22 August 2013. Accepted 12 September 2013.

Abstract

Introduction The physiological effect of posture on intracranial pressure (ICP) is not well described. This study defined and evaluated three mathematical models describing the postural effects on ICP, designed to predict ICP at different head-up tilt-angles from the supine ICP value. Methods Model I was based on a hydrostatic indifference point for the cerebrospinal fluid (CSF) system, i.e. the existence of a point in the system where pressure is independent of body position. Models II and III were based on Davson’s equation for CSF absorption, which relates ICP to venous pressure, and postulated that gravitational effects within the venous system are transferred to the CSF system. Model II assumed a fully communicating venous system and model III that collapse of the jugular veins at higher tilt-angles creates two separate hydrostatic compartments. Evaluation of the models was based on ICP measurements at seven tilt-angles (0-71°) in 27 normal pressure hydrocephalus patients. Results ICP decreased with tilt-angle (ANOVA, p<0.01). The reduction was well predicted by model III (ANOVA lack-of-fit: p=0.65), which showed excellent fit against measured ICP. Neither model I nor II adequately described the reduction in ICP (ANOVA lack-of-fit: p<0.01). Conclusion Postural
Postural effects on intracranial pressure: modeling and clinical evaluation
Sara Qvarlander, Nina Sundström, Jan Malm, Anders Eklund – University of Umeå
Model III – Jugular Vein Collapse

Most closely matches measured ICP

Supine

Implications for VIIP

Conclusion: Posture, gravity, and collapse of the jugular veins influence measured ICP and may influence $R_{out}$

Hypothesis: In zero G, posture is irrelevant and SSSP = CVP because the jugular veins are not collapsed. Normal “venous regulation” of upright ICP is absent. Therefore, based on CVP measurements in zero G, ICP should not be elevated unless during long-duration spaceflight 1) CSF production increases, 2) $R_{out}$ increases, 3) CVP increases, or 4) intracranial fluid volume increases
Intracranial Fluid Volume?

CSF hydrodynamics in idiopathic intracranial hypertension:
A long-term study

Jan Malm, MD; Bo Kristensen, MD; Peter Markgren, MSc; and Jan Ekstedt, MD, PhD

Article abstract—To examine CSF hydrodynamics, we studied 16 patients with idiopathic intracranial hypertension and 45 control subjects with a constant-pressure infusion method. Fifteen patients had 155 examinations up to 15 years after the onset of disease. In most patients, the disturbances of CSF hydrodynamics persisted for many years. We identified at least two mechanisms for the development of the increased CSF pressure: a rise of sagittal sinus pressure, probably explained by extracellular edema causing partial compression of the major venous sinus (type 1), or a low conductance with a compensatory increase in CSF pressure in order to sustain the bulk flow (type 2).

NEUROLOGY 1992;42:851-858

MRI Evidence of Impaired CSF Homeostasis in Obesity-Associated Idiopathic Intracranial Hypertension

Is this really a disorder of ICP?

- From the evidence perspective:
  - The single greatest criticism of NASA’s efforts to date is the meager clinical ICP data
    - Only 4 astronauts have had LPs
    - None have had continuous ICP monitoring
  - The “n” is too small to reach any valid conclusions about ICP and VIIP
  - This is a major flaw in NASA’s approach to studying VIIP
What does NASA need to do?

Stop waiting for the validation of noninvasive ICP methods
- They are unreliable
- They are cumbersome
- The provide only LP equivalence
- They cannot provide continuous ICP monitoring

This is not to say give up on noninvasive ICP, as it is a very desirable method with significant earth-based applications, but the wait is keeping NASA from getting the data it really needs to understand VIIP.
Candidate Noninvasive ICP Methods
IIIH Continuous ICP Recording

Mean ICP measured over several-minute epochs will look normal, even though dynamic ICP is clearly abnormal.
What does NASA need to do?

- Stop hypothesizing and **prove** whether VIIP is or is not a persistent disorder of ICP elevation after return from orbit
- Obtain ICP measurements on as many astronauts as possible using reliable invasive methods
- Obtain continuous ICP measurements in both wakefulness and sleep
- Obtain CSF conductance measurements
What does NASA need to do?

- Find a method for safely and invasively measuring ICP in humans in space
  - Head-down tilt is an unproven model for ICP
    - As described in the report
  - Parabolic flight is too brief and is complicated by rapid swings in $G$, giving only a glimpse of the immediate response to micro-$G$, but no insight into long-term accommodation of ICP
- Noninvasive ICP will have to be compared to invasive ICP in zero $G$ as well as $1 \, G$
What does NASA need to do?

ICP-related VIIP research needs to be organized to answer the critical questions regarding pathophysiologic mechanisms in humans.

Before flight, in space and after return:
- Is ICP elevated?
- Is $R_{out}$ elevated?
- Is CSF production elevated?
- Is CVP elevated?
Long-Term VIIP Research Strategy

- Prove whether CSF circulatory physiology is abnormal
- If so, investigate why
  - Animal models, human studies
  - Any mechanism(s) must explain
    1) The trigger and predisposing factors
    2) Factors that sustain VIIP in orbit, and most importantly
    3) Factors that sustain VIIP after return to earth, which implies a permanent change to the anatomic / physiologic mechanisms of CSF circulation and CSF hydrodynamics
- Identify risk factors by comparing affected and unaffected astronauts
- Identify potential treatments according to the pathophysiologic mechanism(s) (i.e., the need for pharmacologic or interventional treatment)
NASA and NSBRI are constrained by federal law and regulations to pay for research done only by U.S. investigators.

Many of the best investigators who could solve these VIIP questions are outside the U.S.

NASA and NSBRI need to find funding mechanisms, or collaborations with other national space agencies, to recruit and fund the best researchers in the world to work on VIIP.
Thank You